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Review Article

Loneliness and its Relationship with Diabetes Mellitus

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Abstract: Loneliness is highly prevalent globally and has been noted in all age groups. Loneliness is associated with significant physical and mental health risks. These individuals have a poor quality of life. Lonely individuals also demonstrate a high mortality rate and incur more health care costs. Type 2 diabetes mellitus (T2DM). a common chronic disease. Worldwide, it is expected to affect 629 individuals in 2045. Several studies have established an incriminating role of loneliness in the pathogenesis and progression of T2DM. It is estimated that the risk of developing a high HbA1c is almost fivefold in lonely people. This increased risk is independent of other confounding factors. Although increased inflammation and reduced immunity play a role, the main mechanism appears to be an increase in the hypothalamic-pituitary adrenocortical activity. Loneliness also increases unhealthy lifestyles, which also contribute to this deleterious loneliness-diabetes link. Lonely people are also more burdened with chronic diseases, which further increase the diabetic risk and its worsening. They also tend to be more non-adherent to healthcare recommendations. On the other hand, diabetic patients face a multitude of issues with daily living and healthcare, and these tend to increase loneliness. The causative factors and their mechanisms underlying this bidirectional relationship between loneliness and T2DM is narratively reviewed in this manuscript.

Keywords: Loneliness, diabetes mellitus, lifestyles, social isolation, chronic diseases.

INTRODUCTION

Loneliness is a subjective negative feeling resulting from qualitative or quantitative discrepancy between an individual's desired and actual social relationships while social isolation is an objective lack of social contacts [1-3]. These terms are often used interchangeably in the academic literature, but most of the studies are on loneliness and its detrimental association with physical and mental health. The feeling of loneliness is ubiquitous in our society [4]. It is common in high-income as well as low-income and middle-income countries [5-7]. Data show that about 30 million adults in Europe experience loneliness6. Data from the USA indicates that it is also pervasive in this society [7]. It is present in all age groups [7-11]. Several studies have found that it is common in children and adolescents [7, 8]. A 2018 survey by the Kaiser Family Foundation found that 22% of USA adults [aged 18 and older) felt lonely [9]. A study conducted by the American Association of Retired Persons (AARP) Foundation reported that 35 percent of adults in the USA, aged 45 and older were lonely [10]. The National Health and Aging Trends Study found that in community-dwelling adults aged 65 or older, 24% were socially isolated [11]. A recent study by Cigna (a US-based insurance company) of adults aged 18 and older in the USA found that 46% reported "sometimes or always feeling alone [12]".

Loneliness is not a benign condition [13-31]. It aggravates multiple physical health conditions like CVDs [13, 14], obesity [15], several cancers [16, 17], chronic obstructive pulmonary disease [18], arthritis [19], depression [20], and dementia [21]. Lonely individuals are also more susceptible to infections [22]. Loneliness is often associated with a host of psychiatric disorders including depression [23], anxiety [24], alcoholism [25], suicidal ideation [26], impulsivity, and aggressive behavior [27]. Lonely individuals report poor self-rated health [28] and a poor quality of life [29]. Their overall mortality is increased [30, 31]. Loneliness is also strongly linked with type 2 diabetes mellitus (T2DM).

Diabetes mellitus is a common chronic disease [32-38]. The two major types of diabetes are type I and type 2 [32]. Type I is an autoimmune disorder, with several genetic, epigenetic, and environmental factors playing a role in its genesis [33]. Type 2 is due to defective insulin secretion by pancreatic β-cells and/or

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the inability of insulin-sensitive tissues to respond to insulin [34]. Type 2 accounts for 90-95% of all diabetes cases [35]. Its global prevalence, especially in low- and middle-income countries is unfortunately on the rise [36]. Most cases of T2DM occur during the person's prime of life – three of four patients suffering from T2DM are between the ages of 20–64 years [37]. Globally, T2DM affected 425 million in 2016 and this number is expected to reach 629 million by 2045 [38].

According to the American Diabetes Association (ADA) [39], T2DM is diagnosed when the following parameters are met: fasting plasma glucose level of 126 mg/dL (7.0 mmol/L) or higher; 2-hour plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher during a 75-g oral glucose tolerance test; a random plasma glucose of 200 mg/dL (11.1 mmol/L) or higher in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis; or a hemoglobin A1c (HbA1c) level of 6.5% (48 mmol/mol) or higher. Prediabetes is diagnosed by an impaired fasting glucose level of 100 mg/dl to 125 mg/dl (5.6–6.9 mmol L) or impaired glucose tolerance levels of 140 mg/dl to 199 mg/dl (7.8–11.0 mmol L) or an HbA1c 5.7% - 6.4% (39–46 mmol L [40]. Many patients with prediabetes will go on to develop full-fledged T2DM [41]. Type 2 diabetes mellitus is not a benign disease and causes significant microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (coronary artery disease, stroke, and peripheral artery disease) complications [42-46]. A significant number of these patients experience mobility loss and have difficulty with working, resulting in long-term work disability [47]. Diabetes mellitus also causes increased mortality [48, 49]. It is estimated that T2DM causes 1.5 million annual deaths worldwide and contributes to an additional 17.5 million deaths each year [48]. Deaths from T2DM have increased by more than 60% since 2000 and now rank in the top 10 causes of death [49]. These deaths are usually premature and reduce the life expectancy of the affected individual by approximately six years [50]. Prediabetes is also associated with a higher risk of atherosclerotic disease and all-cause mortality [51]. T2DM is an expensive disease and is responsible for approximately 10%-12% of global health expenditure [52, 53]. T2DM by itself increases the risk of developing loneliness – indicating a bidirectional relationship.

Loneliness is usually measured using the UCLA Brief Loneliness Scale [54]. The scale asks three questions: "How often do you feel that you lack companionship?", "How often do you feel left out?", and "How often do you feel isolated from others?" Each item has the response choices of "Hardly ever," "Some of the time," and "Often," and these are assigned scores of 0, 1, and 2 respectively. These scores are summed to arrive at a total score. Higher scores indicate greater loneliness. This scale compares well with the full UCLA Loneliness Scale and has reasonable internal consistency When evaluating loneliness, some researchers have used a single question, such as 'Do you feel lonely?'[55]. 'Do you suffer from loneliness?'[56] or 'Are you ever bothered by feelings of loneliness? [57]. This single question-based diagnosis is also extremely reliable and correlates highly with the two most widely used loneliness assessment tools, the UCLA Loneliness Scale [58] and the de Jong Gierveld Loneliness Scale [59].

DISCUSSION

Loneliness and T2DM are intricately linked [60-62]. Type 2 diabetes mellitus is more common in patients with loneliness60. In the Maastricht Study (a population-based cohort study (n = 2,861), the prevalence of T2DM was higher in socially isolated (SI) individuals [60]. A recent Danish survey (N = 24,687) showed that loneliness and SI were independently associated T2DM (loneliness: adjusted hazard ratio (AHR) =1. 90; SI: AHR = 1.59 [61]. Diabetics are also lonelier. Hackett *et al*. found that 25% of patients with T2DM scored 45 or higher out of a possible 80 on the ULCA scale, indicating loneliness. This score is higher than that reported in non-diabetics: 37.06 for men and 36.06 for women [62]. The relationship between loneliness and T2DM is complex, and each condition increases the risk of others.

Loneliness causing DM

Loneliness is a risk factor for T2DM [63]. Lonely people are more prone to develop metabolic syndrome [64, 65]. A 2010 study found that each 1-unit increase in loneliness was associated with a 10% increase in the odds of a person meeting the criteria for metabolic syndrome [66]. Type 2 diabetes mellitus is a frequent consequence of this syndrome [67]. Scientific studies indicate that there is a relationship between loneliness and elevated glycated hemoglobin (HnA1c) [68, 69]. In one study that looked at the elderly, a high percentage of lonely individuals demonstrated increased levels of HbA1c [69]. Overall, it is estimated that the risk of developing a high HbA1c is almost fivefold in lonely people [69]. Other studies have found that this link between loneliness and diabetes is independent of other confounding factors, such as age, sex, ethnicity, wealth, smoking status, physical activity, alcohol consumption, body mass index (BMI), and CVDs [70].

Lifestyles: Lifestyles play an important role in influencing T2DM71. Healthy lifestyles include not smoking, maintaining a body mass index of 18.5-24.9, regular moderate to vigorous physical activity (≥30 minutes/day), none or low to moderate alcohol intake (not exceeding in women: 5-15 g/day and in men 5-30 g/day), and a higher quality of diet [72]. Lonely individuals often practice unhealthy and risky lifestyles as they have a diminished capacity to adequately regulate their feelings, emotions, and behavior [73-76]. Unhealthy lifestyle behaviors deleteriously impact the development and progression of diabetes mellitus in

these individuals [77]. Their relationship with T2DM is discussed below:

Smoking: Lonely people smoke more [78-81]. Once addicted, they have a harder time giving up smoking [82]. Smokers exhibit a higher risk of developing T2DM. This increased risk ranges from 11.7% in male smokers to 2.4% in female smokers [83]. Even passive smokers show an increased risk of incident T2DM [83]. Smoking also increases microvascular and macrovascular complications in these patients. Smoking is associated with the premature development of neuropathy, nephropathy, and retinopathy [84]. In a meta-analysis of prospective studies on diabetes, Qin *et al*. reported that smoking increased the risk of death in diabetics due to coronary heart disease by 54% and stroke by 44% [85]. Smoking cessation gradually decreases the risk of developing T2DM in those without the disease and vascular complications in those with an established disease [96]. Smoking impacts T2DM by impairing beta-cell function, increasing insulin resistance, and raising inflammatory markers [87]. Smoking on the other hand can also induce loneliness [88, 89].

Alcohol: Lonely people are more likely to drink [90-94]. Several studies have shown that low to moderate intake of alcohol may help in reducing the incidence of T2DM95-99. Low to moderate alcohol intake reduces inflammation, increases insulin sensitivity, and stimulates the synthesis of high-density lipoproteins [100-102]. Heavy alcohol intake, on the other hand, has been associated with a higher risk for T2DM [103, 104] and an increase in its complications [105]. A reduction in alcohol intake in heavy drinkers reduces the risk of T2DM development and improves overall survival [106, 107]. Loneliness, besides being linked with overall alcohol intake, also contributes to excess alcohol consumption and worsening of prognosis [108]. Lonely people often lack social support, and this may aggravate alcohol abuse [109]. On the other hand, alcoholics also tend to be more lonely [108]. These individuals often have a general feeling of life dissatisfaction [110]. This is partially due to a more negative attitude towards oneself and one's social interactions. These feelings encourage loneliness in patients [110].

Obesity: Loneliness enhances obesity [111]. Lonely people eat more energy-dense foods, are less physically active, sleep poorly, eat more at night, and have poor daytime functioning [112-114]. The result is excess body weight. It is estimated that more than 80%-85% of T2DM patients are overweight or obese [115]. Obesity increases the risk of developing T2DM in all age groups [116-119]. Weight loss is beneficial in reducing this risk and is also associated with sustained remission in many established sufferers [120,121]. Clinically, the result is the need for fewer medications, lower hospitalization rates, and reduced complications [122-124]. These patients also experience a better quality of life and increased survival. On the other hand, obesity often causes or aggravates loneliness [125]. Obese individuals may face isolation due to not complying with societal norms [126]. This stigma affects most aspects of their life, including at school, at work, and even at church, further encouraging loneliness [127-129].

Physical Activity: Lonely people exhibit more sedentary behavior and are less likely to partake in regular physical exercise [130-134]. Exercise can help prevent or delay T2DM [135-139] and can reduce complications [140]. Exercise makes diabetics function better and live longer [140]. Exercise helps reduce obesity, blood glucose, HbA1c, triglycerides, and insulin resistance in these patients [141]. It also helps reduce loneliness. In one study involving 382 participants, exercise was associated with a 6.9% decrease in loneliness and a 3.3% improvement in social connectedness [142].

Diet: There is a link between loneliness and poor dietary patterns. These individuals not only consume more calories, (resulting in obesity) but also eat poor quality foods [143-147]. The diabetes obesity link has been discussed earlier in this manuscript. Studies indicate that a poor-quality diet may result in a threefold increase in T2DM risk [148]. Healthy diets, which are primarily plant-based, such as the DASH and the Mediterranean diets show an inverse relationship with T2DM [149, 150].

Following the five healthy lifestyle behaviors mentioned in this manuscript significantly helps decrease T2DM morbidity and mortality [151].

Chronic Diseases: Besides impacting healthy lifestyles, loneliness is linked with T2DM by many other mechanisms. Lonely individuals are more likely to develop other chronic diseases [152], and these conditions may also influence the development and/or worsening of T2DM [37,153,154]. For example, both coronary artery disease and stroke significantly increase mortality in patients with diabetes [155,156]. Secondly, loneliness may worsen the patient's perception of their disease (T2DM), making them feels worse than non-lonely people [157, 158]. Thirdly, lonely individuals with high levels of loneliness may also end up decreasing their self-management ability resulting in non-compliance with therapeutic modalities [159, 160]. The result is a poorer prognosis and an increase in their mortality [161].

Mechanisms: The biological mechanisms linking loneliness with poor health are postulated to be primarily related to the neuroendocrine system [162]. Loneliness results in an increased hypothalamic-pituitary adrenocortical activity [163, 164], diminished immunity [165, 166], and under-expression of genes

bearing anti-inflammatory glucocorticoid responses, and upregulation of pro-inflammatory gene transcripts [167], and abnormal ratios in the circulating white blood cells168. Harmful metabolic changes are also frequently seen [169, 170].

DM causing loneliness

Although studies show that lonely individuals are more likely to suffer from T2DM, the reverse is also true. Patients with diabetes tend to be lonelier. It is estimated that almost one-fifth (16%) of this population experiences intense loneliness [171]. This occurs even in the presence of strong family and social support [172]. Individuals also report higher levels of loneliness if receiving insulin therapy [173]. Kobos *et al*. found a relationship between complications and increased loneliness in these patients [37]. Diabetics with leg complications (peripheral artery disease, ulcers, amputations, etc.) are unable to ambulate freely, increasing their frustration, depression, and loneliness [174, 175]. These complications also cause strain on marital, family, and friend relationships [176-178], which further initiates or aggravates loneliness [179, 180]. Although this manuscript is mainly focused on T2DM, it is important to note that patients with type 1 diabetes also experience significant levels of loneliness [181, 182]. Barnard and Lloyd reported that this incidence was almost double, with 40% of women with type 1 diabetes experiencing loneliness compared to 21% of women with T2DM [183].

CONCLUSION

The prevalence of loneliness has increased in today's world. commensurate with late marriages, increased two-income households, increased residence in single-family homes, and increased digital connectivity [184-186]. As discussed above, loneliness is not only pervasive in our society, but it also has a harmful association with T2DM. Loneliness generates significant metabolic and neurological changes that increase the risk of T2DM. Lonely individuals are also less compliant with healthy lifestyles. This also increases the risk of T2DM directly as well via the increased incidence of other chronic diseases. Diabetic patients are also at an increased risk of developing loneliness. They often feel "alone" and "excluded from society". They feel that there is a lack of understanding by friends, family, healthcare workers, and society. This leads to poor compliance and a worse prognosis in these patients. Currently, there is no pharmacological treatment for loneliness [187]. Approach to alleviate it revolves mainly around efforts to enhance social integration in these individuals. Cognitive behavioral therapy has been successfully used in some patients. A decrease in loneliness improves health/health-related behaviors, diabetes self-management, and a decreased morbidity/mortality in these patients.

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